a reasonable expectation of success in trying a FMV 34S promoter. Alternatively, Applicants submit the Sanger Declaration to rebut the prima facie case and to demonstrate that the cited combination was not obvious at the time the invention was made and that the FMV 34S promoter provides unexpected results.

II. Amendments to Claims

Claim 20 has been amended to state that construct components are operably joined, as suggested by the Patent Office. New Claim 43, submitted in place of cancelled Claim 29, includes similar language.

Claims 24-26 have been amended to refer to the promoter region as upstream of the TATTTAA site, as was stated in Claims 8-10 as originally filed. Applicants note that the original claim language incorrectly included sequence 3' to the TATTTAA region in the stated promoter sizes. The current language correctly recites the numbers of bases upstream of the TATTTAA region that were used in exemplified constructs. Support for the 34S promoter regions recited in Claims 24 and 25 is found at page 9, lines 1-10 (196bp and 362bp upstream from TATTTAA, respectively). Support for the 34S promoter region recited in Claim 26 finds support at page 8, lines 14-15 and in Figure 4. Although the number of base pairs is not specifically stated in the specification, one skilled in the art would readily determine that the indicated *Eco*RI site (first 6bp of Figure 4 sequence] is 892bp 5' of the TATTTAA site at bases 894 to 900 of Figure 4.

Additional amendments to Claims 20, 22-26, 30 and 35-36 are in response to various rejections raised in the Office Action. Support for new Claim

43 is found in Claims 13-14 as filed, and in the specification at page 7, beginning at line 20.

Claims 21 and 31 have been cancelled in view of amendment to Claim 20 and the language of new Claim 43. Claims 32 and 37-42 have been cancelled in the interest of furthering prosecution of the instant application.

It is readily apparent that no new matter is added in the above amendments to the claims, and the Examiner is respectfully requested to enter them in the instant application. These amendments are believed to place the claims in condition for allowance, and in any event are necessary to put the application in better condition for appeal. The amendments were not earlier presented because a Final Office Action was mailed on March 4, 1993, exactly ninety days after the case was filed. Applicants were preparing a Preliminary Amendment at the time that the Final Rejection was received. The arguments and declaration submitted herewith do not raise any new issues which would require a new search. The Examiner is requested to enter this amendment in the interests of efficient prosecution of this application.

III. 35 U.S.C. § 112, Second Paragraph Rejection

Claims 20-42 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

The rejection of Claim 20 is believed avoided by the above amendment to Claim 20 which states that the components are operatively joined and provides a 3' transcript termination region as a component of the transcription constructs. Similar language is presented in new Claim 43 submitted in place of cancelled Claim 29.

The rejection of Claim 22 is believed avoided by amendment to replace "untranslated end" with --flanking region--.

Amendments to Claims 24-26 replace "upstream" with --5' region-- for purposes of clarification, and remove the phrase "approximately". In addition, comments at page 3 of the Office Action and discussions during the Examiner interview as to the use of the term "promoter" were considered in amendments to Claims 24-26. The amendments clarify that Applicants' invention includes constructs which comprise the promoter region upstream of the TATTTAA, as stated in Claims 8-10 as originally filed. As noted by the Examiner in the Office Action of March 19, 1992 and discussed in the Examiner interview, the sizes of the promoter regions originally stated in Claims 8-10 were incorrect, as they referred to the promoter plus a portion of the 5' untranslated region. The rejection of Claims 33-34 is respectfully traversed as these claims now correctly refer to recombinant constructs that "further comprise a 5' untranslated leader sequence", in view of the above discussed amendment to Claim 20.

The rejection of Claims 29-32 is believed avoided in new Claim 43, and Claim 30, dependent thereon. Claim 43 clarifies that the instant invention includes a DNA cassette which comprises two chimeric gene constructs, a first construct wherein a DNA sequence of interest is regulated by an 34S promoter region, and a second DNA construct wherein a DNA sequence of interest is regulated by a CaMV 35S promoter. As described in the specification at pages 7 and 26, such DNA cassettes are valuable in genetic engineering applications where <u>two strong promoters</u> are required. The use of the non-homologous and CaMV

promoters assures high levels of expression in both DNA constructs and avoids DNA recombination problems that might occur were the 35 promoter to be used in two different constructs. In response to comments in the Office Action, no structural orientation between the and CaMV constructs in the DNA cassette is intended, other than that the components of each promoter construct are operably joined, as stated, so as to provide for transcription of their respective DNA sequences of interest.

IV. 35 U.S.C. § 112, First and Second Paragraphs

The rejection of Claims 20 and 23-26 are believed avoided by amendment of these claims to state a figwort mosaic virus 34S promoter.

V. 35 U.S.C. § 102

The rejection of claims 39-40 under Section 102(b) in view of Richins et al. is rendered moot by the cancellation of these claims without prejudice to their presentation in a subsequent continuation application.

Claims 20-21, 23-27 and 33-34 were rejected under 35 U.S.C. 102(b) as anticipated by Richins et al. This rejection is respectfully traversed as follows.

Prior art anticipates a claim only if every element recited in the claim is disclosed in a single item of prior art. Richins et al. does not fulfill this requirement for the invention as presently claimed. The current claims are directed to recombinant DNA constructs which comprise as operably linked components, a figwort mosaic virus promoter and a DNA sequence of interest heterologous to the FMV promoter. Thus, only DNA constructs which

comprise these elements as operatively joined components could be considered to anticipate the instantly claimed invention. There is no disclosure of such constructs in Richins et al., which merely reports the insertion of FMV *Xba*I fragments into cloning vectors. There is no indication that a figwort mosaic virus *Xba*I fragment comprising the FMV 34S promoter was inserted in position for transcription of the ß-galactosidase gene. Furthermore, this reference clearly does not teach constructs which further comprise a plant functional transcription termination region, as stated in the present claims.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

VI. 35 U.S.C. § 103

The Examiner has finally rejected claims 20-42 under 35 U.S.C. § 103 as being unpatentable over Shah et al and Sanders et al taken with Richins et al and Shepherd et al. Applicants respectfully traverse the rejection on the following grounds.

The Final Rejection states:

> At the time this invention was made, it was obvious to one of ordinary skill in the art to modify the primary references with the teachings of the secondary references in order to obtain high levels of expression of genes of interest in host plant cells with yet another strong viral promoter source. The extensive comparative analogy drawn with CaMV would have led one of ordinary skill in the art to have reasonably expected to obtain high levels of constitutive expression with analogous FMV promoters. (Emphasis added.)

Under §103, "whether a particular combination might be obvious to try is not a legitimate test of

patentability". In Re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Obviousness must be established by consideration of the prior art, as well as the claimed invention, as a whole. The reference must do more than suggest that an innovation "ought to be tried," or is obvious in hindsight; it must itself directly suggest the desirability of a new combination. Richdel Division of Garden America Corp. v. Aqua-Trol Corp., 681 F.Supp. 141, 145 (E.D.N.Y. 1988).

In Ex Parte Goeddel, 5 USPQ2d 1449 (PTO Bd.App. 1987) and Ex Parte Old, 229 USPQ 196, 200 (PTO Bd.App. 1985), the Board held that although the technique underlying hybridoma technology is well recognized, nevertheless, the results obtained by its use clearly are unpredictable. Hybridoma technology is an empirical art in which one of ordinary skill in the art is unable to foresee what particular antibodies will be produced. Since no "expected" results can thus be said to be present, it may be "obvious to try" the Kohler-Milstein technique as applied to malignant renal cells, but the result is unobvious because there is no reasonable expectation of success. The same is true in the present invention. The use of promoters generally to obtain high levels of constitutive expression was known. However, the activity or inactivity of particular viral components is not predictable, and thus there is no reasonable expectation of success.

In Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1207-09 (Fed. Cir. 1991), the Federal Circuit affirmed the district court's finding that plaintiff's patent claims to a purified and isolated DNA sequence encoding human erythropoietin ("EPO") were unobvious because there was not a

reasonable expectation of success in cloning the EPO gene using either the inventor's unique gene probing strategy, or the infringer's alternative monkey gene probe strategy. While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious because there was no reasonable expectation of success.

By the same analogy, in Ex Parte Kranz, 19 USPQ2d 1216, 1218 (PTO Bd.App. 1991), the Board reversed an obviousness rejection of applicants' claim to a process for making a target cell susceptible to lysis by a cytotoxic T lymphocyte. Although the examiner had noted certain phenomena observed by those working in the art, these observations were not only devoid of any suggestion to put the phenomena to practical use but also devoid of advice regarding how to accomplish the necessary attaching procedure set forth in the inventors' claims.

The case most relevant to the instant invention is In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants had transformed a cyanobacteria with an insecticidal gene derived from Bacillus using a photosynthetic promoter originally found in cyanobacteria. A combination of six to seven primary and secondary prior art references clearly disclosed all the elements of the invention including the promoter, the insecticidal gene, the cloning vectors and the techniques for the transformation of host cells. In reversing Board's rejection on obviousness, the Federal Circuit held that none of these references discloses or suggests that cyanobacteria could serve as hosts for the expression of genes encoding Bacillus insecticidal proteins. In view of the uncertainty regarding the biology of

cyanobacteria, the prior art does not convey to those of ordinary skill a reasonable expectation of success in expressing insecticidal genes in cyanobacteria.

In the present application, the Examiner has characterized the "modification" of the primary references as suggested by the prior art, and further that there was a reasonable expectation of success for the "modified art." The Examiner takes the position that the strength and utility of the CaMV 35S promoter and the similarity of FMV to CaMV provided a reasonable expectation of success for the FMB 34S promoter. This position is not supported by the record. The Sanger Declaration submitted herewith addresses whether there was a reasonable expectation of success on two different levels. First, the Sanger declaration challenges the Examiner's assertion that the behavior of CaMV 35S promoter was predictive of success in a FMV promoter system. Secondly, the Sanger Declaration demonstrates that FMV viral titer is not necessarily predictive of desirable FMV promoter strength.

The Sanger declaration clearly illustrates that at the time the invention was made CaMV 35S was the only plant viral promoter that was well characterized, making generalizations from this single system an uncertain process. Even the art cited by the Examiner confirms this as the state of the art. In fact, Richins et al. states that "[u]ntil recently, there has been little information on other members of this group of plant viruses, including FMV, the subject of this communication. This virus appears to be similar to CaMV both biologically and because it has a small double-stranded DNA genome. However, hybridization tests have shown that FMV DNA has little apparent sequence

homology with that of CaMV." (See Richins et al., page 8451, second paragraph continues to page 8452) (emphasis added). This would imply that the apparent similarities were not actual. Indeed, the lack of sequence homology would suggest that the two viruses would behave differently. The Sanger Declaration identifies the ambiguities confronted by even present day investigators who cannot predictably tie sequence homology to functional equivalence. Certainly, based on the state of the art at the time the invention was made, there is no reasonable expectation that different sequences would behave similarly. Therefore, the Examiner cannot establish that it would have been obvious to try FMV 34S with a reasonable expectation of success. Such a conclusion can only be drawn from 20-20 hindsight.

On the issue of viral titer, the Examiner has cited Shepherd et al for the proposition that it would have been obvious to try FMV to obtain a strong promoter: the high titer of FMV generally would have been predictive of a strong FMV promoter. This rationale is without support in the relevant art, and therefore there is no reasonable expectation of success. There is no proven relationship between the strength of a given viral promoter and the aggressiveness of the parent virus in planta. Specific evidence of this unpredictability is the case in point. Since the severity, viral titer and aggressiveness of CaMv is much greater than that of FMV, if viral titer were to be used as an indicator of promoter strength, it would be expected that the FMV 34S promoter would be significantly weaker than the CaMV 35S promoter, but it is not. (Sanger Decl., ¶¶ 8-12.)

Shepherd et al. note that the most striking changes in the genomes of the low and high-titer FMV strains studied were in the region that corresponds to the region VI gene, not in the region that corresponds to the claimed FMV 34S promoter. Moreover, the high strength FMV 34S promoter characterized in the instant application is derived from a low titer strain of FMV (strain M3 discussed in Shepherd et al.), yet has strong promoter activity comparable to that of the higher titer CaMV 35S promoter. Thus, solely focussing on the references of record, there is no basis for the Examiner's contention that FMV viral titer can be used to predict the FMV 34S promoter strength, i.e., that viral titer provides a reasonable expectation of success of the promoter.

The lack of correlation between viral titer and viral promoter strength can be explained at the molecular level. (Richins et al.) It has been established that a retrovirus (i.e, most of plant virus such as CaMV and FMV are retrovirus employing RNA as their genetic material and relying on reverse transcription for converting their RNA into DNA for incorporation into host genome) uses its gag gene for synthesizing requisite protein necessary for encapsidation. Thus, a person of ordinary skill in the virology art would have known that the viral titer is frequently a direct function of the activity of viral gag gene, but does not depend on the strength of viral promoter. Therefore, the Examiner's citation of Shepherd et al. as providing motivation to study FMV as a promoter source based on viral titer determinations is without merit and cannot be reasonably used to suggest promoter

activity for FMV. There is no reasonable expectation of FMV promoter success based on FMV viral titer.

This type of unexpected result (equivalent promoter strength even though CaMV has substantially higher titer than FMV) is exactly the reason why "obvious to try" is not a permissible test for patentability, yielding to patent protection when unexpected results are achieved.

The record as augmented by the Sanger Declaration, now shows that the behavior of viral promoters is generally viewed as unpredictable. Therefore the rejection which must be grounded on a reasonable expectation of success fails.

VII. Monsanto's FMV Promotor Application

Applicant attaches hereto as Exhibit A a published European Patent Application entitled Promotor for transgenic plants. This European application claims priority from U.S. Application Serial NO. 429,917, filed on October 31, 1989. It is directed to figwort mosaic virus promoters. It is not submitted as prior art because the present application is entitled to relate back to the filing date of its grandparent application Serial No. 07/404,283, filed on September 7, 1989.

VIII. Conclusion

This case is now in condition for allowance. The claim language issues have been adequately addressed. The novelty rejections have been met, and all should now be removed. Applicants have presented adequate evidence to demonstrate that the obviousness rejection must also be withdrawn. Applicants invite the Examiner to telephone their undersigned counsel,

if in any way, such a call would expedite issuance of the present application,

Respectfully submitted,

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